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Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fisher Lane, Rm 1061
Rockville, MD 20852

Re: Docket No. 2005D-0240

I have read Guidance for Indusrty. Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention. I would like to offer the following comments.

In 1980 I co-authored a paper " The Modified Papillary Bleeding Index: Comparison with Gingival Index during the Resolution of Gingivitis", J. Prev. Dent, April 1980, 135-138). In that paper we stated that a bleeding index may be a sensitive measure of gingivitis since it gave consistently higher scores than the Gingival Index of Loe and Sillness and the Modified Gingival Index of Lobene. However, from that paper we concluded (p. 138) that "these findings suggest that in order to accurately assess severity and/or changes in gingivitis, bleeding should be one of the primary parameters considered."

Having conducted numerous clinical studies since 1980, we did not use a bleeding index often since we found that it was subject to errors such as probing pressures, how was the probing done (mesial-distal, distal-mesial, gingival margin, interproximal papilla, or intracrevicular.) Also the presence of calculus hampered our ability to record bleeding when the study did not begin with an initial prophylaxis.

Among the modifications of the Gingival Index of Loe and Sillness developed for use in clinical trials were non-invasive indices which used only visual criteria of inflammation, as it was felt that the requirement for physically invading the gingival sulcus could be undesirable in longitudinal clinical trials. Concerns about the use of invasive procedures have been related to the effect of probing on disrupting plaque at the gingival margin, on traumatizing the gingival while inflamed, and the obscuring of specific sites by blood oozing from previously probed areas on the opposite or adjacent tooth surfaces.(Chilton & Fleiss, 1986, Design and analysis of plaque and gingivitis clinical trials, J. Clin. periodontal, 13, 1986, 400-406, Lobene, discussion. Current status of indices for measuring gingivitis, J. Clin Periodontol, 13, 1986, 381-382, and Ciancio, Discussion: biological and measurement issues critical to design of gingivitis trials, J. Perio. Res., 27, 373-374, 1992).

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It is also noteworthy that, in studies in which replicate bleeding scores were obtained, the second set of readings were consistently higher than the first, suggesting that the invasive procedure produced some gingival trauma and/or increased the tendency of the gingival to bleed on provocation. (Birkeland & Jorkjend, the Influence of examination on the assessment of the intra-examiner error by using the plaque and gingival index systems, Community dental and Oral Epidem, 3, 1975, 214-216, Feldman, et al, Inteerexaminer agreement in the measurement of periodontal disease, J. Dent. Res, 64, 1985, 262 , abs. # 787).

In 1984 Dr. Gary Greenstein (primary author of a paper correlating bleeding upon provocation with histological changes in 1981) reviewed the diagnostic importance of bleeding on probing and stated: "bleeding may be a more sensitive clinical sign of gingivitis than changes in color; however, clinicians do see visually inflamed gingival sites which do not bleed upon probing. The latter occurs often enough to preclude one from categorically stating that bleeding is always an earlier sign of inflammation and underscores our lack of understanding of the mechanisms responsible for bleeding" (Greenstein, The role of bleeding upon probing in the diagnosis of periodontal disease. A literature review, J. Periodontol 55, 1984, 684-688).

His comments may be associated with the fact that our population is growing older and taking more and more medications and dietary supplements. One of the side effects of over 500 medications is xerostomia which may result in increased gingival bleeding. Also,gingival bleeding is also a side effect of patients taking a number of herbal substances as well as those taking low dose aspirin as an anticoagulant. In contrast, patients taking non steroidal anti-inflammatory drugs may mask the bleeding aspect of gingivitis. This can also occur in patients taking antibiotics within one month of being enrolled in a study.

In view of medication related problems associated with a bleeding index, enrollment of subjects in a clinical trial would be a major, cumbersome, if not impossible project.

Lastly, when I was an executive officer of the American Academy of Peridontology , a survey study was carried out by Teledyne Water Pik (now Water Pik) which evaluated the impression of the American public about oral health. When they were asked if their gums bled when they flossed or brushed, many of them said yes. However, when they were asked if they had gingivitis, most of them said no. As a matter of fact, in my practice and in my teachings in or clinic, I have to daily tell patients that, if their gums bleed when they floss or brush, this is a sign of gingivitis and they have to clean these areas thoroughly instead of avoiding them (as many of them do when they see bleeding).

In summary, I would like to state that I support the use of visual indices of inflammation such as the Gingival Index of Loe and Sillness or the Modified Gingival Index of Lobene as primary measures of Gingivitis. These indices have been shown to survive the test of time, examiners can be well calibrated with these indices, and they are reliable. If a

bleeding index is incorporated into a study, it should be a secondary index used to corroborate the directional effect seen in the visual index used in the study but, if used, must rule out all medication related factors. Further, since bleeding indices show higher scores than visual indices, changes in them could reflect an overestimate to patients of the potential benefit of a product since they tend to show large reductions I bleeding when used in studies.

Sincerely,

Dr. Sebastian G. Ciancio, Distinguished Service Professor and Chair, Department of Periodontics and Endodontics